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Carbohydrate Research 299 (1997) 271–279

CARBOHYDRATE RESEARCH

Synthesis of 2″-acylamido derivatives of 2″-amino-5,2″-dideoxy-5-epi-5-fluorodibekacin and a study on the structures of 5-fluorinated dibekacin analogs by ^{13}C NMR

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Received 23 October 1996; accepted 7 January 1997

Abstract

Several 2″-amino-2″-deoxy and 2″-acylamido-2″-deoxy derivatives (**15–21**) of 5-deoxy-5-epi-5-fluorodibekacin have been prepared, introducing the 2″-NH_2 group via oxidation–methoxyimination–reduction processes. The C-4 and C-6 chemical shifts in the ^{13}C NMR spectra of several 5-fluorinated kanamycin analogs have been studied, and the difference in shifts was explained on the basis of F-5–O-4 and F-5–O-6 distances estimated by MOPAC93/PM3 calculations on related model compounds. © 1997 Elsevier Science Ltd.

Keywords: 5-Fluorinated dibekacin; 2″-Acylamidation; ^{13}C Chemical shift; F–O Distance

1. Introduction

Dibekacin (3′,4′-dideoxykanamycin B) [1] is a strongly antibacterial aminoglycoside antibiotic and its 1-*N*-[(*S*)-4-amino-2-hydroxybutanoyl] (AHB) derivative (arbekacin) [2] is still more active. However, these clinically used compounds have shortcomings, such as being acetylated or phosphorylated by resistant bacteria at the H_2N-6′ and HO-2″ positions [3], respectively. Their toxicity is also a defect. To overcome these drawbacks, several attempts at structural modification [4–9] have been made, among which substitution of HO-2″ with an NH_2 group provided a compound not phosphorylated at that position [6]. Comparison of stereo models of arbekacin, 1-*N*-(4-amino-2-hydroxybutanoyl)kanamycin A [10], and 1-*N*-[(2*R*,3*R*)-4-amino-3-fluoro-2-hydroxybutanoyl]dibekacin [11] with that of a proposed compound, the 2″-*N*-(4-aminobutanoyl)dibekacin analog, suggested that the amino acid residue of the last compound extends sterically in a direction similar to that of the former compounds having side-chains at H_2N-1 [11]. Preparation of several related 2″-acyl derivatives of 2″-amino-5,2″-dideoxy-5-epi-5-fluorodibekacin [6] was thus undertaken in the hope of obtaining new analogs not susceptible to phosphorylation at the HO-2″ position of arbekacin.

2. Results and discussion

Synthesis.—Penta-*N*-tosyldibekacin (**1**) [7] was converted into its 4″,6″-*O*-benzylidene derivative **2**,

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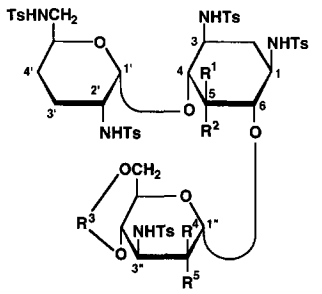
PII S0008-6215(97)00031-1

which was acetylated (to give **3**) and fluorinated with diethylaminosulfur trifluoride (DAST) [12] to give the 5-epi-5-fluoro derivative **4**. The fluorination was useful to avoid oxidation at the C-5 in the next step as well as to enhance the antibacterial activity [13]. Deacetylation of **4** (to give **5**) followed by oxidation with $(CH_3)_2SO$–Ac_2O gave the 2″-oxo derivative **6**.



	R¹	R²	R³	R⁴	R⁵
1	OH	H	H, H	H	OH
2	OH	H	C_6H_5CH	H	OH
3	OH	H	C_6H_5CH	H	OAc
4	H	F	C_6H_5CH	H	OAc
5	H	F	C_6H_5CH	H	OH
6	H	F	C_6H_5CH	=O	
7	H	F	C_6H_5CH	$=NOCH_3$	
8	H	F	C_6H_5CH	H	NH_2
9	H	F	C_6H_5CH	NH_2	H
10	H	F	C_6H_5CH	H	NH·ZAHB
11	H	F	C_6H_5CH	NH·ZAHB	H
12	H	F	C_6H_5CH	H	NH·Zgly
13	H	F	C_6H_5CH	H	NH·Zapa
14	H	F	C_6H_5CH	H	NH·Zaba

ZAHB: $COCH(OH)CH_2CH_2NHCO_2CH_2C_6H_5$

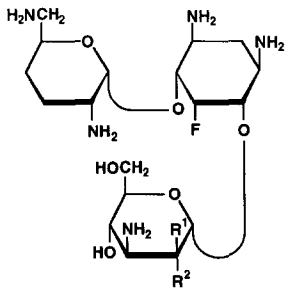
Zgly : $COCH_2NHCO_2CH_2C_6H_5$

Zapa : $COCH_2CH_2NHCO_2CH_2C_6H_5$

Zaba : $COCH_2CH_2CH_2NHCO_2CH_2C_6H_5$

Reductive amination of the oxo group was first attempted with NH_4OAc–$NaBH_3CN$ in methanol; however, it gave only a 2″-hydroxy compound (possibly **5**). Several attempts were made by varying the amounts and the time of addition of the two reagents, but these proved unsuccessful. Changing the solvent from methanol to pyridine, however, gave the 2″-amino derivative **8** without accompaniment by **9** (as described later) but in poor yield (~ 20%). As the structurally similar 3″-*N*-(benzyloxycarbonyl)-2″-oxo derivative [6] was reported to give the corresponding 2″-amino derivative in good yield by conventional reductive amination, the difficulty in amination of **6** may be ascribed to the vicinal TsNH-3″ group. Reduction of **6** was, therefore, tried after conversion into the oxime. The 2″-methoxyimino derivative **7** prepared was treated with $LiBH_4$–$(CH_3)_3SiCl$ according to Banaszek and Karpiesiuk [14], whereupon the 2″-amino compound (**8**) and its 2″-epimer were obtained in a moderate yield in 3:1 ratio. Deprotection of **8** and **9** with Na in liquid NH_3 gave, respectively, the free amines, namely, 2″-amino-5,2″-dideoxy-5-epi-5-fluorodibekacin (**15**) [15] and 2″-amino-5,2″-dideoxy-5,2″-diepi-5-fluorodibekacin (**16**).

The N-protected (*S*)-4-amino-2-hydroxybutanoyl (AHB) residue was next attached to the H_2N-2″ of **8** and **9** utilizing its active ester [16], and the resulting amides (**10** and **11**, respectively) were deblocked to give the 2″-*N*-AHB derivatives **17** and **18**. Similarly, N-protected glycine, β-alanine, and 4-aminobutanoic acid were introduced at the H_2N-2″ position of **8**, and the products (**12**, **13**, and **14**) were deblocked to give the corresponding 2″-*N*-acyl derivatives (**19**, **20**, and **21**), whose structures were confirmed by their ^{13}C NMR spectra (Table 1). All of the C-2″ resonances of the synthetic products were shifted upfield (at ~ 55 ppm) indicating the presence of an N-2″ atom.



15 $R^1 = H$, $R^2 = NH_2$

16 $R^1 = NH_2$, $R^2 = H$

17 $R^1 = H$, $R^2 = NHCOCH(OH)CH_2CH_2NH_2$

18 $R^1 = NHCOCH(OH)CH_2CH_2NH_2$, $R^2 = H$

19 $R^1 = H$, $R^2 = NHCOCH_2NH_2$

20 $R^1 = H$, $R^2 = NHCOCH_2CH_2NH_2$

21 $R^1 = H$, $R^2 = NHCOCH_2CH_2CH_2NH_2$

Structure.— ^{13}C chemical-shift relationships.—Examination of the ^{13}C NMR spectra of **15**–**21** showed that their C-4 signals resonated at higher fields ($\Delta\delta$ 5.5–6 ppm) than those of C-6 (Table 2). In general, in kanamycin analogs having an equatorial HO-5, both C-4 and C-6 have similar shift-values (measured as free bases), reflecting a similar steric environment [17–19]. When, however, the equatorial HO-5 is replaced by an equatorial F, axial F, or diF, both C-4 and C-6 shifted upfield but to different extents, that is, more significantly at C-4 and less at C-6 (Table

Table 1
^{13}C NMR chemical shifts (ppm) of **15–21** measured in 26% ND_3 in D_2O [a]

	15	**16**	**17**	**18**	**19**	**20**	**21**
C-1	48.14 d	47.75 d	48.06 d	47.83 d	47.87 d	48.01 d	48.05 d
C-2	36.43	32.20	36.21	36.28	36.23	36.22	36.18
C-3	47.66 d	47.53 d	47.61 d	47.64 d	47.61 d	47.66 d	47.63 d
C-4	79.18 d	79.02 d	79.02 d	79.07 d	79.07 d	79.08 d	79.06 d
C-5	90.38 d	90.05 d	90.18 d	89.99 d	90.12 d	90.20 d	90.20 d
C-6	84.88 d	84.51 d	84.95 d	84.75 d	85.10 d	85.07 d	85.06 d
C-1′	97.22	97.09	97.14	97.19	97.17	97.18	97.17
C-2′	50.22	50.06	50.16	50.17	50.14	50.18	50.17
C-3′	26.83	26.66	26.75	26.81	26.71	26.76	26.75
C-4′	28.27	28.10	28.21	28.21	28.20	28.24	28.23
C-5′	71.26	71.12	71.17	71.21	71.20	71.23	71.22
C-6′	45.81	45.62	45.73	45.74	45.73	45.77	45.76
C-1″	102.52	104.48	100.08	101.79	100.01	100.08	100.10
C-2″	56.27	54.21	54.32	53.05	54.38	54.58	54.62
C-3″	56.03	52.37	52.93	51.29	52.90	52.69	52.65
C-4″	71.21	68.13	71.30	68.45	71.36	71.36	71.31
C-5″	73.65	74.49	73.57	74.33	73.44	73.46	73.44
C-6″	61.98	61.86	61.80	61.61	61.77	61.83	61.83
C=O			177.64	177.84	176.38	175.68	177.21
C-2‴			70.35	70.44	44.32	39.06 [b]	33.87
C-3‴			37.09	37.15		38.00 [b]	29.01
C-4‴			37.97	37.86			40.99

[a] $J_{C,F}$ are $J_{C\text{-}1,F}$ 3.5–3.8, $J_{C\text{-}3,F}$ 3.8–4, $J_{C\text{-}4,F} \approx J_{C\text{-}6,F}$ 16.7–17, $J_{C\text{-}5,F}$ 177 Hz.
[b] Interconvertible.

2). This means that the β-effect caused by the conversion of the HO-5*eq* to the more electron-withdrawing fluorine(s) is larger at C-4 than at C-6. This tendency was also observed in the present study, as already described. The reason for this phenomenon is, however, not clear. As F-5*ax* gives a different effect from that of F-5*eq* [13], electronegativity and orientation of the fluorine at C-5 may be the cause. However, a reverse effect was observed in 5-epi-netilmicin [8] (see Table 2), which showed a larger

Table 2
^{13}C NMR chemical shifts (ppm) of fluorinated kanamycin analogs and netilmicin analogs [8] at C-4 and C-6 measured in 20–26% ND_3 in D_2O (expressed by the upfield shifts from the standard values)

Substituent at C-5		C-4	C-6	Nr of compounds	Ref.
	Kanamycins [a]	0	0		
	(OH-5*eq*)	(86.8–89.1; av 88.0)	(88.4–89.2; av 88.6)	9	[4,17–19]
Axial F		8.9–9.1 [b]	3.6–3.7 [c]	2	[13]
		8.8–9.0 [b]	3.5–4.1 [c]	7 (**15–21**)	This paper
DiF		6.2–6.4 [b]	4.3 [c]	2	[7]
Equatorial F		4.3–4.5 [b]	2.7–2.8 [c]	3	[7]
	Netilmicin [a]	0	0		[8]
		(86.7)	(85.5)		
DiF [d]		6.1 [b]	2.9 [c]	1	[8]
Equatorial F [e]		4.0 [b]	1.3 [c]	1	[8]
Axial OH (epinetilmicins)		2.6–2.7 [b]	4.6–4.8 [c]	2	[8]

[a] Reference compounds.
[b] Upfield shift ($\Delta\delta$, ppm) based on 88.0 or 86.7 ppm (for netilmicin analogs).
[c] Upfield shift ($\Delta\delta$, ppm) based on 88.6 or 85.5 ppm (for netilmicin analogs).
[d] 5-Deoxy-5,5-difluoronetilmicin.
[e] 5-Deoxy-5-fluoronetilmicin.

upfield shift at C-6 than at C-4 (netilmicin has a 2-deoxy-1-*N*-ethylstreptamine moiety instead of the 2-deoxystreptamine present in kanamycins).

To clarify this result, electron-densities at C-4 and C-6 of several model compounds, namely, dibekacin (**A**), 5-epi- (**B**), 5-deoxy-5-fluoro- (**C**), 5-deoxy-5-epi-5-fluoro- (**D**), and 5-deoxy-5,5-difluoro-dibekacins (**E**) were calculated [20] by using MOPAC93/PM3; however, no correlation of the densities at C-4 and C-6 was observed in the foregoing compounds, precluding this possibility. As magnetic shielding (deshielding) of ^{13}C nuclei is determined by diamagnetic, paramagnetic (these predominate in ^{13}C nuclei and relate to electron-density), and neighboring-group-(or -molecule-)participation items [21,22], the experimental shift-difference was predicted to be derived from the third item. Consequently, further study examined the energy-minimum conformations of **A**–**E**; however, no correlation was seen between the actual shifts in our synthetic compounds and the inter-moiety angles (usually termed ϕ and φ), or charge-distributions in particular atoms in **A**–**E**. However, the results obtained relative to the distances of F-5–O-4 and F-5–O-6 in the model compounds (Table 3) were promising; the former was always shorter than the latter, which agrees with the experimental result that C-4 always resonated at higher field than C-6. This means that, in D_2O–ND_3, a through-space interaction in F-5–O-4 (or O-6) may operate to shield the vicinal carbons at C-4 and C-6, closer to the F–O atoms, and stronger in effect. These distance-related results (Table 3) also show good agreement with the order of upfield shifts of our synthetic compound, that is, C-4 (ax-F) > C-4 (diF) > C-4 (eq-F) ≥ C-6 (diF) > C-6 (ax-F) > C-6 (eq-F) (Table 2) is inversely proportional to the order of distances, O-4 (ax-F) < O-4 (diF; F-ax is taken as the value) < O-4 (eq-F) < O-6 (diF) = O-6 (ax-F) < O-6 (eq-F) (abbreviations are used to facilitate the comparison with these data; see Table 3). These results may also be applicable to the netilmicin series (Table 2). It should be noted that 5-epinetilmicins, which are similar in structure to 5-epidibekacin (**B**), show larger upfield shifts at C-6 than at C-4 (Table 2), and this agrees with the negative difference in O–O distances in **B** (Table 3). This may relate to the fact that the *HO-5ax* hydrogen in **B** is located closer to O-4 (*OHax*–O-4 2.47 Å, which is in a range for hydrogen-bonding interaction [23]) than to O-6 (*OHax*–O-6 3.68 Å), although a similar tendency was also observed in **A**. The small shift-differences in kanamycins having HO-5*eq* also reflect the small difference in O–O distances in **A**.

Antibacterial activity.—The synthesized products, except for **15**, showed only limited antibacterial activity or were devoid of such activity (see Experimental section). This indicates that attachment of an ω-amino acid at H_2N-2″ of **8** had no desirable effect, confirming that 1-*N*-acylation is not substituted by 2″-*N*-acylation. Moreover, it was established that epimerization of the H_2N-2″ group of **15** (to give **16**) greatly decreases the antibacterial activity.

3. Experimental

General methods.—TLC was performed on Silica Gel 60 F_{254} (E. Merck 5715), with detection under UV light at 254 nm, by charring with aq 50% H_2SO_4, or by 0.4% ninhydrin in pyridine. Column chromatography was performed on Wakogel C-300. Optical rotations were determined with a Perkin–Elmer

Table 3
Distances (Å) of F-5–O-4 (or O-5–O-4) and F-5–O-6 (or O-5–O-4) for model compounds **A**–**E** determined by MM2UEC refined by MOPAC93/PM3

Substituent at C-5		Compound [a]	F-5–O-4 (O-4) [b]	F-5–O-6 (O-6) [b]	Difference
Axial F		**D**	2.71	2.77	0.06
DiF	ax	**E**	2.73	2.77	0.04
	eq	**E**	2.76	2.85	0.09
Equatorial F		**C**	2.75	2.84	0.09
			O-5–O-4	O-5–O-4	
Axial OH		**B**	2.85	2.81	−0.04
Equatorial OH		**A**	2.89	2.91	0.02

[a] **A**, **B**, **C**, **D**, **E** are the model compounds, respectively, for kanamycin analogs having HO-5*eq* [4,17–19], 5-epinetilmicin [8], 5-deoxy-5-fluoro-kanamycin B's [7] and -netilmicin [8], 5-deoxy-5-epifluorokanamycin B's [13], 5-deoxy-5,5-difluoro-kanamycin B's [7] and -netilmicin [8] (see also Table 2).
[b] O-4 And O-6 are the abbreviations for F-5–O-4 and F-5–O-6, respectively (see text).

241 polarimeter. NMR spectra (^{1}H at 250 and 500 MHz, ^{13}C at 125.8 MHz, ^{19}F at 235 and 470.5 MHz) were recorded with Bruker AC-250P and AMX-500 spectrometers, using Me_4Si or $CFCl_3$ (for ^{19}F) as the internal reference. Proton signals were mostly confirmed by the ^{1}H–^{1}H COSY.

4″, 6″ - O - Benzylidene - 1, 3, 2′, 6′, 3″ - penta - N - tosyldibekacin (**2**).—A mixture of **1** (12.25 g, 10.0 mmol), $C_6H_5CH(OMe)_2$ (4.5 mL, 30 mmol), and TsOH (620 mg, 3.6 mmol) in dry DMF (130 mL) was stirred at 50 °C overnight, poured into aq $NaHCO_3$ (3 L, satd), and the resulting precipitate was filtered, washed thoroughly with water and hexane, and dried (at 50 °C in vacuo under P_2O_5) to give **2** as a solid (13.12 g, quant), $[\alpha]_D^{23}$ +22° (*c* 1, DMF). Anal. Calcd for $C_{60}H_{71}N_5O_{18}S_5$: C, 54.99; H, 5.46; N, 5.34; S, 12.23. Found: C, 55.23; H, 5.67; N, 5.43; S, 11.76.

2″-O-Acetyl-4″,6″-benzylidene-1,3,2′,6′,3″-penta-N-tosyldibekacin (**3**).—A mixture of **2** (13.1 g, 10.0 mmol) and AcCl (1.42 mL, 20 mmol) in pyridine (130 mL) was stirred vigorously (~ 30 min) and allowed to stand at room temperature for 3 h. After water (6 mL) was added, the soln was concd to a small volume, poured into water (2.5 L), and the precipitate was filtered off, washed with water, and dried. Chromatography (15:1 $CHCl_3$–MeOH) of the solid gave **3** as a solid (11.5 g, 84%), $[\alpha]_D^{22}$ +17° (*c* 1, $CHCl_3$); ^{1}H NMR (pyridine-d_5) (only selected signals were shown): δ 2.12, 2.15, 2.17, 2.32, 2.33, 2.49 [each s of 3 H, 5 Ts(Me) and one Ac], 3.55 (m, 1 H, H-5), 5.51 (d, 1 H, H-1′), 5.60 (s, 1 H, C*H*Ph), 5.65 (dd, $J_{1'',2''}$ 3.5, $J_{2'',3''}$ 10 Hz, H-2″), 5.88 (d, 1 H, H-1″). Anal. Calcd for $C_{62}H_{73}N_5O_{19}S_5 \cdot H_2O$: C, 54.33; H, 5.52; N, 5.11. Found: C, 54.31; H, 5.44; N, 4.96.

2″-O-Acetyl-4″,6″-O-benzylidene-5-deoxy-5-epi-5-fluoro-1,3,2′,6′,3″-penta-N-tosyldibekacin (**4**).—To a soln of **3** (10.40 g, 7.6 mmol) in CH_2Cl_2 (200 mL) was added DAST (3.0 mL, 15 mmol), and the soln was kept at room temperature for 2.5 h. Aqueous $NaHCO_3$ (200 mL, satd) was added under vigorous stirring, and the separated organic layer was dried (Na_2SO_4) and concd. The residue was chromatographed (15:1 $CHCl_3$–MeOH) to give **4** as a solid (8.53 g, 83%), $[\alpha]_D^{22}$ +27° (*c* 1, $CHCl_3$); ^{1}H NMR (pyridine-d_5): δ 2.14, 2.17, 2.20, 2.23, 2.30, 2.34 [each s of 3 H, 5 Ts(Me) and Ac], 3.54 (m, 1 H, H-2′), 3.65 (br t, 1 H, H-1 or 3), 4.05 (m, 1 H, H-6 or 4), 4.09 (m, 1 H, H-3 or 1), 4.09 (m, 1 H, H-4 or 6), 4.64 (t, 1 H, H-3″), 5.39 (d, 1 H, H-1′), 5.52 (dd, 1 H, H-2″), 5.54 (s, 1 H, C*H*Ph), 5.56 (d, 1 H, H-1″), 5.82 (d, 1 H, $J_{5,F}$ 52 Hz, H-5). ^{19}F NMR (pyridine-d_5): δ −212.95 (dt, *J* 28, 28, 52 Hz, F-5). Anal. Calcd for $C_{62}H_{72}FN_5O_{18}S_5$: C, 54.97; H, 5.36; N, 5.17; S, 11.84. Found: C, 54.75; H, 5.09; N, 5.01, S, 11.81.

4″,6″-O-Benzylidene-5-deoxy-5-epi-5-fluoro-1,3,2′,6′,3″-penta-N-tosyldibekacin (**5**).—A soln of **4** (8.13 g, 6.0 mmol) in a 1:60 mixture of 28% NaOMe in MeOH and MeOH (100 mL) was kept at room temperature for 1 h. After concn, the residue dissolved in $CHCl_3$ was washed with water, dried (Na_2SO_4), and concd. The residue was chromatographed ($CHCl_3$ → 20:1 $CHCl_3$–MeOH) to give **5** as a solid (6.85 g, 87%), $[\alpha]_D^{22}$ +26° (*c* 1, DMF) and −5° (*c* 1, pyridine); ^{1}H NMR (pyridine-d_5): δ 2.07, 2.16, 2.17, 2.20, 2.34 [each s of 3 H, 5 Ts(Me)], 4.34 (dd, 1 H, H-2″), 4.46 (dd, 1 H, H-3″), 5.40 (s, 1 H, C*H*Ph), 5.43 (m, 2 H, H-1′, 1″), 5.83 (d, 1 H, H-5). ^{19}F NMR (pyridine-d_5): δ −212.34 (dt, *J* 28, 28, 52 Hz, F-5). Anal. Calcd for $C_{60}H_{70}FN_5O_{17}S_5$: C, 54.90; H, 5.38; N, 5.33; S, 12.21. Found: C, 54.68; H, 5.39; N, 5.51; S, 12.32.

4″,6″-O-Benzylidene-5,2″-dideoxy-5-epi-5-fluoro-2″-oxo-1,3,2′,6′,3″-penta-N-tosyldibekacin (**6**).—A soln of **5** (2.5 g, 1.9 mmol) in a mixture of Me_2SO (25 mL) and Ac_2O (12.5 mL) was heated at 50 °C for 30 min. After concn to ~ 1/3 volume in vacuo, the soln was poured into aq $NaHCO_3$ (30 mL, satd), and the precipitate was filtered off, washed with water, and dried. Chromatography ($CHCl_3$ → 20:1 $CHCl_3$–MeOH) of the solid and the fractions showing a spot of R_f 0.3 (TLC with 15:1 $CHCl_3$–MeOH) were collected, washed with water, dried (Na_2SO_4), and concd to give **6** as a solid (1.48 g, 58%), $[\alpha]_D^{23}$ +38° (*c* 1, $CHCl_3$); ^{1}H NMR (pyridine-d_5; measured after the soln was kept at 50 °C overnight in the presence of molecular sieves 4 Å): δ 2.10, 2.17, 2.20, 2.23, 2.27 [each s of 3 H, 5 Ts(Me)], 3.56 (dq, 1 H, H-2′), 3.99 (t, 1 H, H-6″a), 4.01 (m, 1 H, H-1 or 3), 4.07 (dd, 1 H, H-4″), 4.13 (dd, 1 H, H-4 or 6), 4.16 (dd, 1 H, H-6 or 4), 4.25 (m, 1 H, H-3 or 1), 4.71 (dt, 1 H, H-5″), 5.03 (dd, 1 H, H-6″b), 5.27 (dd, 1 H, H-3″), 5.40 (s, 1 H, C*H*Ph), 5.42 (d, 1 H, H-1′), 5.60 (s, 1 H, H-1″), 5.87 (d, 1 H, H-5), 8.42 (t, 1 H, *J* 6 Hz, TsN*H*-6′), 9.06 (d, 1 H, *J* 9 Hz, TsN*H*-3 or 1), 9.27 (d, 1 H, *J* 7 Hz, TsN*H*-1 or 3), 9.32 (d, 1 H, *J* 8 Hz, TsN*H*-2′), 10.02 (d, 1 H *J* 8 Hz, TsN*H*-3″); $J_{1,6} \approx J_{3,4}$ 11, $J_{4(6),F}$ 28, $J_{5,F}$ 52, $J_{1',2'}$ 4, $J_{3'',4''} \approx J_{4'',5''} \approx J_{5'',6''a} \approx J_{6''a,6''b}$ 10, $J_{5'',6''b}$ 5 Hz. ^{19}F NMR (pyridine-d_5): δ −213.2 (dt, ~0.5 H, F-5 for the 2″-oxo form), −212.1 (dt, ~0.5 H, F-5 for the hydrate form; disappeared on addition of molecular sieves); $J_{5,F}$ 52, $J_{4,F} \approx J_{6,F}$ 26 Hz. ^{13}C NMR (pyridine-d_5;

measured after addition of molecular sieves): δ 21.16, 21.18, 21.21, 21.29, 21.32 [5 Ts(CH_3)], 24.22 (C-3′), 27.95 (C-4′), 36.55 (C-2), 47.50 (C-6′), 51.02 and 51.08 (each d, $J_{C\text{-}1(3),F}$ 5 Hz, C-1, C-3), 52.87 (C-2′), 63.02 (C-3″), 65.50 (C-5″), 67.75 (C-5′), 69.07 (C-6″), 77.79 and 81.11 (d, $J_{C\text{-}4\ (or\ 6),F}$ 17.5 and 18 Hz, respectively, C-4, 6), 81.68 (C-4″), 90.12 (d of $J_{C\text{-}5,F}$ 184 Hz, C-5), 98.43 (C-1′), 101.70 (C-1″), 101.86 (CHPh), 195.13 (C-2″); C-2″ appeared at δ 107.26 in addition to 195.13 before addition of molecular sieves. Anal. Calcd for $C_{60}H_{68}FN_5O_{17}S_5 \cdot 2H_2O$: C, 53.51; H, 5.39; N, 5.20; S, 11.90. Found: C, 53.35; H, 5.03; N, 5.67; S, 11.78.

*4″,6″-*O*-Benzylidene-5,2″-dideoxy-5-epi-5-fluoro-2-(methoxyimino)-1,3,2′,6′,3″-penta-*N*-tosyldibekacin* (**7**).—A mixture of **6** (200 mg, 0.15 mmol), $NH_2OMe \cdot HCl$ (63 mg, 0.75 mmol), and molecular sieves 3 Å (50 mg) in dry pyridine (4 mL) was heated at 70 °C for 15 h; $NH_2OMe \cdot HCl$ (32 mg) and molecular sieves 3 Å (25 mg) were added, and the mixture was heated for a further 40 h. Evaporation left a residue, which was dissolved in $CHCl_3$, and the soln was successively washed with aq 10% $KHSO_4$ and aq $NaHCO_3$ (satd), dried (Na_2SO_4), and concd. The residue (202 mg, quant for **7**) showed, on TLC (15:1 $CHCl_3$–MeOH), an R_f value of 0.5 along with R_f 0.6 [very weak spot; the minor oxime isomer (?)]. The product was used, without purification, for the next step. For an analytical sample, it was purified by chromatography (20:1 $CHCl_3$–MeOH), $[\alpha]_D^{22}$ +34° (*c* 1, $CHCl_3$); ^{1}H NMR (pyridine-d_5): δ 2.14, 2.17, 2.20, 2.26, 2.29 [each s of 3 H, 5 Ts(Me)], 3.55 (m, 1 H, H-2′), 3.70 (s, 3 H, $NOCH_3$), 3.77 (m, 1 H, H-1 or 3), 3.92 (dd, 1 H, H-6″a), 3.95 (t, 1 H, H-4″), 4.12 (dd, 1 H, H-6 or 4), 4.13 (dd, 1 H, H-4 or 6), 4.23 (m, 1 H, H-3 or 1), 4.46 (dt, 1 H, H-5″), 5.02 (dd, 1 H, H-6″b), 5.17 (dd, 1 H, H-3″), 5.43 (d, 1 H, H-1′), 5.61 (s, 1 H, C*H*Ph), 5.82 (d, 1 H, $J_{5,F}$ 51 Hz, H-5), 6.29 (s, 1 H, H-1″); $J_{1,6} \approx J_{3,4}$ 10, $J_{4(6),F}$ 28, $J_{5,F}$ 51, $J_{1',2'}$ 3, $J_{3'',4''} \approx J_{4'',5''} \approx J_{5'',6''a} \approx J_{6''a,6''b}$ 10, $J_{5'',6''b}$ 5, $J_{3'',NH}$ 8 Hz. ^{19}F NMR (pyridine-d_5): δ −213.2 (dt, *J* 28, 28, 52 Hz, F-5). ^{13}C NMR (pyridine-d_5): δ 25.45 (C-3″), 29.26 (C-4′), 37.33 (C-2), 48.82 (C-6′), 52.20 and 52.45 (d, $J_{C\text{-}1\ (or\ 3),F}$ 5.1 and 4.7 Hz, C-1,3), 54.13 (C-2′), 56.77 (C-3′), 63.91 ($NOCH_3$) 66.72 (C-5″), 68.96 (C-5′), 70.22 (C-6″), 79.31 [d, $J_{C\text{-}4\ (or\ 6),F}$ 17.8 Hz, C-4 (or 6)], 81.03 (C-2″), 82.37 (C-4″), 82.40 [d, $J_{C\text{-}6\ (or\ 4),F}$ 17.9 Hz, C-6 (or 4)], 91.56 (d, $J_{C\text{-}5,F}$ 184 Hz, C-5), 95.06 (C-1″), 99.83 (C-1′), 103.21 (CHPh). Anal. Calcd for $C_{61}H_{71}FN_6O_{17}S_5 \cdot H_2O$: C, 53.96; H, 5.42; N, 6.19; S, 11.81. Found: C, 54.19; H, 5.36; N, 6.46; S, 11.82.

*2″-Amino-4″,6″-*O*-benzylidene-5,2″-dideoxy-5-epi-5-fluoro-1,3,2′,6′,3″-penta-*N*-tosyldibekacin* (**8**) *and 2″-amino-4″,6″-*O*-benzylidene-5,2″-dideoxy-5,2″-diepi-5-fluoro-1,3,2′,6′,3″-penta-*N*-tosyldibekacin* (**9**).—To a mixture of $LiBH_4$ (26 mg, 1.2 mmol) in cold (−20 °C) dry THF (3 mL) was added Me_3SiCl (0.38 mL, 3.0 mmol) under N_2, and the mixture was stirred at room temperature for 2 h. To the suspension cooled to −20 °C was added a soln of **7** (162 mg, 0.12 mmol) in THF (0.5 mL), and the mixture was stirred under N_2 at room temperature overnight. In TLC (10:1 $CHCl_3$–MeOH), the organic layer showed spots of R_f 0.65 (**7**), 0.26 (**9**), 0.24 (**8**), 0.05 (minor), and 0 (minor). The mixture was poured into aq $NaHCO_3$ (satd, 4 mL), concd, and the residue was extracted with THF. The extracted product was chromatographed (silica gel 30 mL, 15:1 $CHCl_3$–MeOH) to give **8** (64 mg, 40%) and **9** (23 mg, 14%) as solids.

Compound **8**: $[\alpha]_D^{22}$ +29° (*c* 1, DMF); ^{1}H NMR (pyridine-d_5): δ 2.14, 2.16, 2.20, 2.27, 2.31 [each s of 3 H, 5 Ts(Me)], 3.31–3.36 (m, 2 H, H-6′a, 2″), 3.41 (dt, 1 H, H-6′b), 3.54 (dddd, 1 H, *J* 3, 4, 8, 11 Hz, H-2′), 3.76 (t, 1 H, H-4″), 4.09 (m, 1 H, H-3″), 5.25 (d, 1 H, $J_{1'',2''}$ 4 Hz, H-1″), 5.39 (s, 1 H, C*H*Ph), 5.41 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1′), 5.83 (br dt, *J* ~1, ~1, 51 Hz, H-5). ^{19}F NMR (pyridine-d_5): δ −212.74 (dt, *J* 28, 28, 51 Hz, F-5). Anal. Calcd for $C_{60}H_{71}FN_6O_{16}S_5 \cdot H_2O$: C, 54.20; H, 5.53; N, 6.32; S, 12.06. Found: C, 54.10; H, 5.63; N, 6.63; S, 11.95.

Compound **9**: $[\alpha]_D^{22}$ +40° (*c* 1, DMF); ^{1}H NMR (pyridine-d_5): δ 2.14, 2.17, 2.20, 2.24, 2.29, [each s of 3 H, 5 Ts(Me)], 3.30–3.41 (m, 2 H, H-6′a, 6′b), 3.58 (m, 1 H, H-2′), 3.68 (d, 1 H, $J_{2'',3''}$ 4 Hz, H-2″), 4.39–4.44 (m, 2 H, H-3″, 5″), 5.25 (s, 1 H, H-1″), 5.38 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1′), 5.50 (s, 1 H, C*H*Ph), 5.84 (d, 1 H, $J_{5,F}$ 51 Hz, H-5). ^{19}F NMR (pyridine-d_5): δ −212.61 (dt, *J* 28, 28, 51 Hz, F-5). Anal. Calcd for $C_{60}H_{71}FN_6O_{16}S_5 \cdot H_2CO_3$: C, 53.34; H, 5.36; N, 6.12; S, 11.67. Found: C, 53.37; H, 5.59; N, 6.28; S, 11.57.

*4″,6″-*O*-Benzylidene-2″-[(*S*)-4-(benzyloxycarbonylamino)-2-hydroxybutanoylamido]-5,2″-dideoxy-5-epi-5-fluoro-1,3,2′,6′,3″-penta-*N*-tosyldibekacin* (**10**) *and its 2″-epimer* (**11**).—To a soln of **8** (107 mg, 0.08 mmol) in 3:1 4-dioxane–H_2O (1.1 mL) were added *N*-[(*S*)-4-(benzyloxycarbonylamino)-2-hydroxybutanoyloxy]succinimide [16] (56 mg, 0.16 mmol) and Na_2CO_3 (17 mg, 0.16 mmol), and the soln was kept at 50 °C for 3.5 h. Evaporation left a residue, which was extracted with $CHCl_3$. The soluble matter was chromatographed (12:1 $CHCl_3$–MeOH) to give **10** as a solid (91.2 mg, 73%) along with **8** recovered

(27 mg). Compound **10**: $[\alpha]_D^{22}$ +60° (*c* 1, $CHCl_3$). Similar treatment of **9** (110 mg, 0.08 mmol) gave **11** as a solid (86 mg, 70%) along with **9** (30 mg). Compound **11**: $[\alpha]_D^{22}$ +30° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{72}H_{84}FN_7O_{20}S_5$: C, 55.91; H, 5.47; N, 6.34; S, 10.36. Found: compound **10**, C, 55.95; H, 5.73; N, 6.21; S,10.51. Compound **11**, C, 55.64; H, 5.65; N, 6.23; S, 10.16.

Condensation of **8** *with* N-*(benzyloxycarbonyl)-glycine (Zgly), 3-(benzyloxycarbonylamino)propanoic acid (Zapa), and 4-(benzyloxycarbonylamino)butanoic acid (Zaba) to give* **12**, **13**, *and* **14**, *respectively.* —To a mixture of **8** (80 mg, 0.06 mmol) and Zgly (25.5 mg, 0.12 mmol) [Zapa (27 mg, 0.12 mmol) or Zaba (22 mg, 0.09 mmol)] in THF (1.6 mL) were added Et_3N [27 μL, 0.12 mmol (27 μL, 0.12 mmol or 20 μL, 0.09 mmol)] and water-soluble carbodiimide [$EtN{=}C{=}N(CH_2)_3NMe_2 \cdot HCl$] [23.4 mg, 0.12 mmol (23.4 mg, 0.12 mmol or 17 mg, 0.09 mmol)], and the mixture was kept at 50 °C for 2 h (2 h or 8 h). Evaporation left a residue, the soln of which in $CHCl_3$ was successively washed with aq 10% $KHSO_4$, aq $NaHCO_3$ (satd), and water, dried (Na_2SO_4), and concd. The residue was chromatographed with 12:1 (15:1 or 12:1) $CHCl_3$–MeOH to give **12** (80.7 mg, 89%), **13** (82.4 mg, 90%), and **14** (74.4 mg, 81%) as solids, respectively.

Compound **12**: $[\alpha]_D^{23}$ +68° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{70}H_{80}FN_7O_{19}S_5$: C, 55.95; H, 5.37; N, 6.52; S, 10.67. Found: C, 55.80; H, 5.45; N, 6.60; S, 10.50.

Compound **13**: $[\alpha]_D^{23}$ +57° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{71}H_{82}FN_7O_{19}S_5$: C, 56.22; H, 5.45; N, 6.46; S, 10.57. Found: C, 56.03; H, 5.49; N, 6.57; S, 10.53.

Compound **14**: $[\alpha]_D^{22}$ +69° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{72}H_{84}FN_7O_{19}S_5$: C, 56.49; H, 5.53; N, 6.41; S, 10.47. Found: C, 56.46; H, 5.74; N, 6.15; S,10.29.

2″-Amino-5,2″-dideoxy-5-epi-5-fluorodibekacin (**15**). —To a soln of **8** (100 mg, 0.075 mmol) in liquid NH_3 (~ 15 mL) at −55 °C was added Na (~ 60 mg), and the deep-blue soln was kept at this temperature for 15 min. Powdered NH_4Cl was added until the soln became colorless, and the NH_3 was evaporated off. The residue was charged onto a column of Amberlite CG 50 (NH_4^+ form) and, after the column was washed with water, the product was eluted with aq 0.1 → 0.4 M NH_3 (gradually raised) to give **15** as a solid, $[\alpha]_D^{23}$ +130° (*c* 1, H_2O) (only antibacterial data was reported [16]); ^1H NMR (26% ND_3 in D_2O): δ 2.63 (dd, 1 H, $J_{1'',2''}$ 3.5, $J_{2'',3''}$ 10.5 Hz, H-2″), 2.78 (dt, 1 H, $J_{1',2'} \approx J_{2',3'eq}$ 3.5, $J_{2',3'ax}$ 12 Hz, H-2′), 2.81 (dd, 1 H, $J_{2'',3''}$ 10.5, $J_{3'',4''}$ 9.5 Hz, H-3″), 3.44 (ddd, 1 H, *J* 2, 10, 30 Hz, H-6), 3.57 (ddd, 1 H, *J* 2, 10, 29 Hz, H-4), 4.94 (d, 1 H, H-1′), 4.98 (d, 1 H, H-1″), 5.38 (br dt, 1 H, *J* 2, 2, 52 Hz, H-5). ^{19}F NMR (26% ND_3 in D_2O): δ −213.79 (ddd, *J* 29, 30, 52 Hz, F-5). Anal. Calcd for $C_{18}H_{37}FN_6O_6 \cdot 0.7H_2CO_3$: C, 45.29; H, 7.80; N, 16.95; F, 3.83. Found: C, 45.42; H, 7.76; N, 17.16; F, 3.62.

2″-Amino-5,2″-dideoxy-5,2″-diepi-5-fluorodibekacin (**16**).—Compound **9** (79.5 mg, 0.058 mmol) was treated as described for **15** to give **16** as a solid monocarbonate (17.8 mg, 60%), $[\alpha]_D^{23}$ +100° (*c* 1, H_2O); ^1H NMR (26% ND_3 in D_2O): δ 2.81 (ddd, 1 H, *J* 3, 4, 12 Hz, H-2′), 3.00 (dd, 1 H, $J_{2'',3''}$ 4, $J_{3'',4''}$ 10 Hz. H-3″), 3.21 (d, 1 H, $J_{2'',3''}$ 4 Hz, H-2″), 3.36 (t, 1 H, $J_{3'',4''} \approx J_{4'',5''}$ 10 Hz, H-4″), 3.49 (ddd, 1 H, *J* ~ 1, 10, 29 Hz, H-6), 3.53 (ddd, 1 H, *J* ~ 1, 10, 29 Hz, H-4), 4.95 (s, 1 H, H-1″), 4.96 (d, 1 H, H-1′), 5.37 (br dt, 1 H, *J* ~ 1, ~ 1, 52 Hz, H-5). ^{19}F NMR (26% ND_3 in D_2O): δ −214.04 (dt, *J* 29, 29, 52 Hz, F-5). Anal. Calcd for $C_{18}H_{37}FN_6O_6 \cdot H_2CO_3$: C, 44.35; H, 7.64; N, 16.33; F, 3.69. Found: C, 44.39; H, 7.83; N, 16.43; F, 3.50.

2″-[(S)-4-Amino-2-hydroxybutanoylamido]-5,2″-dideoxy-5-epi-5-fluorodibekacin (**17**).—Compound **10** (57.5 mg, 0.037 mmol) was treated as described for **15** to give **17** as a solid sesquicarbonate (12.0 mg, 50%), $[\alpha]_D^{22}$ +93° (*c* 1, H_2O); ^1H NMR (26% ND_3 in D_2O): δ 1.64–1.72 (m, 3 H, H-3′*eq*, 4′*eq*, 3‴a), 1.86 (m, 1 H, H-3‴b), 2.69 (t, 2 H, *J* 7, 7 Hz, H-4‴a,b), 2.75 (ddd, 1 H, *J* 3, 4, 12 Hz, H-2′), 3.06 (dd, 1 H, $J_{2'',3''}$ 11, $J_{3'',4''}$ 9.5 Hz, H-3″), 3.22 (t, 1 H, *J* 9.5, 9.5 Hz, H-4″), 3.38 (br dd, 1 H, *J* ~ 1, 10, 29 Hz, H-6), 3.47 (br dd, 1 H, *J* ~ 1, 10, 29 Hz, H-4), 3.81–3.86 (m, 3 H, H-2″, H-5″, H-6″b), 4.21 (dd, 1 H, *J* 4, 9 Hz, H-2‴), 4.90 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1′), 4.97 (d, 1 H, $J_{1'',2''}$ 3.5 Hz, H-1″), 5.33 (br dt, 1 H, *J* ~ 1, ~ 1, 53 Hz, H-5). ^{19}F NMR (26% ND_3 in D_2O): δ −213.74 (dt, *J* 29, 29, 53 Hz, F-5). Anal. Calcd for $C_{22}H_{44}FN_7O_8 \cdot 1.5H_2CO_3$: C, 43.65; H, 7.33; N, 15.16; F, 2.94. Found: C, 43.38; H, 7.10; N, 15.00; F, 2.74.

2″-[(S)-4-Amino-2-hydroxybutanoylamido]-5,2″-dideoxy-5,2″-diepi-5-fluorodibekacin (**18**).—Compound **11** (182.4 mg, 0.118 mmol) was treated similarly to the way described for **15** to give **18** as a solid (30.0 mg, 39%), $[\alpha]_D^{23}$ +60° (*c* 1, H_2O); ^1H NMR (26% ND_3 in D_2O): δ 1.66–1.72 (m, 3 H, H-3′*eq*, 4′*eq*, 3‴a), 1.86 (m, 1 H, H-3‴b), 2.70 (t, 2 H, H-4‴a,b), 2.76 (ddd, 1 H, *J* 3, 4, 12 Hz, H-2′), 3.19

(dd, 1 H, $J_{2'',3''}$ 4, $J_{3'',4''}$ 9.5 Hz, H-3″), 3.35 (t, 1 H, H-4″), 3.44 (ddd, 1 H, $J \sim 1$, 10, 29 Hz, H-6), 3.48 (ddd, 1 H, $J \sim 1$, 10, 28 Hz, H-4), 4.24 (dd, 1 H, J 4, 8 Hz, H-2‴), 4.35 (dd, 1 H, $J_{1'',2''}$ 1, $J_{2'',3''}$ 4 Hz, H-2″), 4.90 (br s, 1 H, H-1″), 4.91 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1′), 5.30 (br dt, 1 H, $J \sim 1$, ~ 1, 52 Hz, H-5). ^{19}F NMR (26% ND_3 in D_2O): δ −213.92 (ddd, J 28, 29, 52 Hz, F-5). Anal. Calcd for $C_{22}H_{44}FN_7O_8 \cdot 1.5H_2CO_3$: C, 43.65; H, 7.33; N, 15.16; F, 2.94. Found: C, 43.29; H, 7.44; N, 14.92; F,2.97.

5, 2″ - Dideoxy - 5 - epi - 5 - fluoro - 2″ - glycylamidodibekacin (**19**).—Compound **12** (52.0 mg, 0.035 mmol) was treated as described for **15** to give **19** as a solid carbonate · hemihydrate (10.8 mg, 54%), $[\alpha]_D^{23}$ +122° (*c* 1, H_2O); ^{1}H NMR (26% ND_3 in D_2O): δ 2.80 (ddd, 1 H, J 3, 4, 12 Hz, H-2′), 3.04 (dd, 1 H, $J_{2'',3''}$ 11.5, $J_{3'',4''}$ 9 Hz, H-3″), 3.27 (t, 1 H, J 9, 9 Hz, H-4″), 3.31 (d, 1 H, J 16 Hz, H-2‴a), 3.38 (d, 1 H, J 16 Hz, H-2‴b), 3.41 (ddd, 1 H, J 2, 10, 28 Hz, H-6), 3.57 (ddd, 1 H, J 2, 10, 28 Hz, H-4), 3.85–3.90 (m, 3 H, H-2″, 5″, 6″b), 4.95 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1′), 5.02 (d, 1 H, $J_{1'',2''}$ 4 Hz, H-1″), 5.38 (br dt, 1 H, $J \sim 1$, ~ 1, 53 Hz, H-5). ^{19}F NMR (26% ND_3 in D_2O): δ −213.70 (dt, J 28, 28, 53 Hz, F-5). Anal. Calcd for $C_{20}H_{40}FN_7O_7 \cdot H_2CO_3 \cdot 0.5H_2O$: C, 43.43; H, 7.46; N, 16.88. Found: C, 43.75; N, 7.19; N, 16.51.

2″-(3-Aminopropanoylamido)-5,2″-dideoxy-5-epi-5-fluorodibekacin (**20**).—Compound **13** (54.4 mg, 0.036 mmol) was treated as described for **15** to give **20** as a solid tricarbonate (12.6 mg, 50%), $[\alpha]_D^{23}$ +112° (*c* 1, H_2O); ^{1}H NMR (26% ND_3 in D_2O): δ 2.41–2.52 [m, 2 H, H-2‴a, H-2‴b (or H-3‴a, H-3‴b)], 2.83 (ddd, 1 H, J 3, 4, 12 Hz, H-2′), 2.90 [m, 2 H, H-3‴a, 3‴b (or 2‴a, 2‴b)], 3.06 (dd, 1 H, $J_{2'',3''}$ 11, $J_{3'',4''}$ 9.5 Hz, H-3″), 3.28 (t, 1 H, J 9.5, 9.5 Hz, H-4″), 3.44 (ddd, 1 H, J 2, 10, 30 Hz, H-6), 3.55 (ddd, 1 H, J 2, 10, 29 Hz, H-4), 3.87–3.93 (m, 3 H, H-2″, 5″, 6″b), 4.97 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1′), 5.05 (d, 1 H, $J_{1'',2''}$ 4 Hz, H-1″), 5.41 (br dt, 1 H, $J \sim 2$, ~ 2, 52 Hz, H-5). ^{19}F NMR (26% ND_3 in D_2O): δ −213.65 (ddd, J 29, 30, 52 Hz, F-5). Anal. Calcd for $C_{21}H_{42}FN_7O_7 \cdot 3H_2CO_3$: C, 40.62; H, 6.82; N, 13.82; F, 2.68. Found: C, 40.78; H, 6.99; N, 14.37; F, 2.87.

2″-(4-Aminobutanoylamido)-5,2″-dideoxy-5-epi-5-fluorodibekacin (**21**).—Compound **14** (38.8 mg, 0.025 mmol) was treated as described for **15** to give **21** as a solid tricarbonate (12.3 mg, 67%), $[\alpha]_D^{21}$ +95° (*c* 1, H_2O); ^{1}H NMR (26% ND_3 in D_2O): δ 1.68–1.78 (m, 4 H, H-3′*eq*, 4′*eq*, 3‴a, 3‴b), 2.27–2.38 (m, 2 H, H-2‴a, 2‴b), 2.61 (t, 2 H, J 7 Hz, H-4‴a, 4‴b) 2.80 (ddd, 1 H, J 3, 4, 12 Hz, H-2′), 3.04 (dd, 1 H, $J_{2'',3''}$ 11, $J_{3'',4''}$ 9 Hz, H-3″), 3.25 (t, 1 H, J 9, 9 Hz, H-4″), 3.41 (ddd, 1 H, J 2, 10, 30 Hz, H-6), 3.52 (ddd, 1 H, J 2, 10, 29 Hz, H-4), 3.83–3.90 (m, 3 H, H-2″, 5″, 6″b), 4.94 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1′), 5.01 (d, 1 H, $J_{1'',2''}$ 4 Hz, H-1″), 5.38 (br dt, 1 H, $J \sim 2$, ~ 2, 52 Hz, H-5). ^{19}F NMR (26% ND_3 in D_2O): δ −213.63 (dt, J 29, 29, 52 Hz, F-5). Anal. Calcd for $C_{22}H_{44}FN_7O_7 \cdot 3H_2CO_3$: C, 41.49; H, 6.96; N, 13.55. Found: C, 41.26; H, 7.00; N, 13.73.

Minimal inhibitory concn (μg / mL) of dibekacin, **15**, **16**, **17**, **18**, **19**, **20**, *and* **21**.—Performed on Mueller–Hinton agar at 37 °C for 18 h. *Staphylococcus aureus* Smith: 0.39, 6.25, 6.25, 12.5, 25, 25, 25, A, in the following order; *S. aureus* Ap01: A, 50, 50, A, A, A, A, A; *S. epidermidis* 109: 1.56, 6.25, 6.25, 50, A, A, A, A; *Escherichia coli* K-12: 3.13, 12.5, 12.5, 50, A, 50, A, A; *E. coli* K-12 ML 1629: 6.25, 25, 25, A, A, A, A, A; *Klebsiella pneumoniae* PCI 602: 3.13, 25, 25, A, A, A, A, A; *Serratia marcescens*: 6.25, 50, 50, A, A, A, A, A; *Pseudomonas aeruginosa* A3: 1.56, 12.5, 12.5, A, A, A, A, A (A: 100 or > 100).

Acknowledgements

The authors are grateful to Dr. Yoshihiko Kobayashi at our Institute for carrying out the computations.

References

[1] H. Umezawa, S. Umezawa, T. Tsuchiya, and Y. Okazaki, *J. Antibiot.*, 24 (1971) 485–487; S. Umezawa, H. Umezawa, Y. Okazaki, and T. Tsuchiya, *Bull. Chem. Soc. Jpn.*, 45 (1972) 3624–3628.

[2] S. Kondo, K. Iinuma, H. Yamamoto, K. Maeda, and H. Umezawa, *J. Antibiot.*, 26 (1973) 412–415.

[3] S. Kondo, A. Tamura, S. Gomi, Y. Ikeda, T. Takeuchi, and S. Mitsuhashi, *J. Antibiot.*, 46 (1993) 310–315.

[4] R. Kuwahara and T. Tsuchiya, *Carbohydr. Res.*, 286 (1996) 107–122.

[5] R. Kuwahara and T. Tsuchiya, *Carbohydr. Res.*, 293 (1996) 15–30.

[6] S. Kondo, S. Shibahara, T. Usui, T. Kudo, A. Tamura, S. Gomi, Y. Ikeda, D. Ikeda, and T. Takeuchi, *J. Antibiot.*, 46 (1993) 531–534.

[7] T. Shitara, Y. Kobayashi, T. Tsuchiya, and S. Umezawa, *Carbohydr. Res.*, 232 (1992) 273–290.

[8] E. Umemura, T. Tsuchiya, Y. Koyama, and S. Umezawa, *Carbohydr. Res.*, 238 (1993) 147–162.

[9] T. Tsuchiya, T. Shitara, S. Umezawa, T. Takeuchi, M. Hamada, N. Tomono, and E. Umemura, *Carbohydr. Res.*, 240 (1993) 307–312.

[10] T. Naito, S. Nakagawa, Y. Narita, S. Toda, Y. Abe, M. Oka, H. Yamashita, T. Yamasaki, K. Fujisawa, and H. Kawaguchi, *J. Antibiot.*, 27 (1974) 851–858.
[11] Y. Takahashi, C. Ueda, T. Tsuchiya, and Y. Kobayashi, *Carbohydr. Res.*, 249 (1993) 57–76.
[12] L.N. Markovskii, V.E. Pashinnik, and A.V. Kirsanov, *Synthesis*, (1973) 787–789; M. Hudlicky, *Org. React.*, 35 (1988) 513–637; J.A. Wilkinson, *Chem. Rev.*, 92 (1992) 505–519.
[13] T. Shitara, E. Umemura, T. Tsuchiya, and T. Matsuno, *Carbohydr. Res.*, 276 (1995) 75–89.
[14] A. Banaszek and W. Karpiesiuk, *Carbohydr. Res.*, 251 (1994) 233–242.
[15] S. Kondo, *Jpn. J. Antibiot.*, 47 (1994) 561–574.
[16] H. Kawaguchi, T. Naito, S. Nakagawa, and K. Fujisawa, *J. Antibiot.*, 25 (1972) 695–708.
[17] Y. Takahashi, T. Tsuchiya, S. Umezawa, and H. Umezawa, *Carbohydr. Res.*, 210 (1991) 221–232.
[18] Y. Kobayashi, T. Tsuchiya, T. Ohgi, N. Taneichi, and Y. Koyama, *Carbohydr. Res.*, 230 (1992) 89–105.
[19] Y. Takahashi, S. Tsuneda, T. Tsuchiya, Y. Koyama, and S. Umezawa, *Carbohydr. Res.*, 232 (1992) 89–105.
[20] A. El Nemr, T. Tsuchiya, and Y. Kobayashi, *Carbohydr. Res.*, 293 (1996) 31–59.
[21] E. Breitmaier and W. Voelter, *^{13}C NMR Spectroscopy*, 2nd ed., Verlay Chemie, Weinheim, 1978, pp 69–70.
[22] H.O. Kalinowski, S. Berger, and S. Braun, *Carbon-13 NMR Spectroscopy*, Engl. ed., Wiley, Chichester, 1986, pp 92–96.
[23] Y. Kobayashi and T. Tsuchiya, *Carbohydr. Res.*, submitted.